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The Effect of A-3826G Polymorphism of Uncoupling Protein-1 on Visceral Fat Area in Overweight Korean Women

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Abstract

Uncoupling protein-1 (UCP-1) plays a major role in thermogenesis, and has been implicated in the pathogenesis of obesity and metabolic disorders. The aim of this study was to estimate the effects of A-3826G polymorphism of UCP-1 gene on body fat distribution. Two hundred forty eight Korean female overweight subjects with BMI more than 25 kg/m^2 participated in this study. The areas of abdominal subcutaneous and visceral fat of all subjects were measured from computed tomography cross sectional pictures of the umbilical region. Subcutaneous fat areas of upper and lower thigh were also measured. Body composition was measured by bio-impedance analysis, and serum concentrations of biochemical parameters, such as glucose, triglyceride, cholesterol etc, were also measured. Genotype of UCP-1 was analyzed by polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP) method. The frequencies of UCP-1 genotypes were AA type; 27.8%, AG type; 51.2% and GG type; 21.0%, and the frequency of G allele was 0.47. Body weight, BMI, WHR, SBP, DBP and body compositions were not significantly different by UCP-1 genotype. Abdominal visceral fat area was significantly higher in AG and GG type compared with AA type ($p=0.009$), but subcutaneous fat areas were not significantly different by UCP-1 genotype. Among biochemical parameters, LDL cholesterol level was significantly higher in GG type compared with AA and AG types ($p=0.033$). Among all subjects, 121 subjects finished 1 month weight loss program containing hypocaloric diet and exercise. The reduction of body weight and BMI were lower in GG type compared with AA/AG type even though statistical significances were not found ($p>0.05$). These results suggest that UCP-1 genotype has a significant effect on visceral fat accumulation among Korean female overweight subjects with BMI more than 25 kg/m^2.

Key words: uncoupling protein-1, polymorphism, visceral fat, computed tomography, LDL cholesterol

INTRODUCTION

Obesity is a complex disease, which results from the interaction of several environmental and genetic factors. The Uncoupling protein 1 (UCP-1) gene, which is one of the candidate genes suggested to play a role in the development of obesity, is a mitochondrial proton transporter dissipating energy through heat instead of ATP synthesis. Its expression was firstly reported in brown adipose tissue (BAT) which was reported to play important roles for energy homeostasis in rodent (1-3). Recently, it was recently reported that UCP-1 mRNA and protein was detected in white adipose tissue of mouse and human (4,5). Esterbauer et al. (6) measured UCP-1 mRNA level in peritoneal adipose tissues obtained from fat biopsy of 153 morbid obese subjects, and found that UCP-1 mRNA expression levels were significantly lower in morbidly obese subjects than in lean subjects.

The human UCP-1 gene has been located to the long arm of chromosome 4 (7), and A→G polymorphism at position -3826 (A-3826G) in the distal promoter region of UCP-1 gene was found from Quebec Family Study in 1994 (8). Until now, many studies were conducted in various populations to elucidate the association of A-3826 polymorphism with obesity phenotypes (9-17). Kogure et al. (9) reported that this polymorphism was associated with reduction during low calorie diet, and Heilbronn et al. (12) showed that -3826 G variant of UCP-1 was significantly associated with increased BMI in overweight Australian women.

However, few studies were conducted about the effects of A-3826G polymorphism of the UCP-1 on body fat distribution. This study was conducted to elucidate the

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effects of this polymorphism on computed tomography (CT)-measured abdominal and distal fat distribution along with metabolic index among Korean female overweight subjects with BMI more than 25 kg/m^2.

MATERIALS AND METHODS

Subjects

Two hundred forty eight Korean female overweight subjects with BMI more than 25 kg/m^2 were recruited from Kirin Oriental Medical Hospital (Seoul, Korea). The general characteristics of the subjects were listed in Table 1. Genomic DNA was obtained with informed consent. Body compositions were measured by bio-impedance analysis using a commercial device (Inbody 2.0, Biospace Co., Korea). The areas of abdominal subcutaneous and visceral fat of all subjects were measured from CT cross-sectional pictures of the umbilical region as described (18). The subcutaneous fat areas at upper and lower thigh were also measured using CT (Hispeed CT/e, GE, USA). Among all subjects, 121 subjects finished 1 month weight loss program composed of 800 kcal/day hypocaloric diet and aerobic exercise, and the changes in body weight and BMI during the program were measured.

Determination of the UCP-1 genotype

Genomic DNA was extracted from whole blood using a Qiagen mini kit (QIAGEN Inc., Valencia CA., USA). PCR reactions were conducted to amplify a genomic DNA fragment containing A-3826G position of UCP-1 gene. Upstream primer (5'CCAGTGGTGGCTAATGAGAGAA3'), downstream primer (5'GCACAAAGAAGAAG-CAGA GAGG3'), 3 μL dNTP mix (1 mM), 0.2 μL Taq DNA polymerase (1 unit) and 3 μL PCR buffer (10×) were added and adjusted to total volume of 30 μL with distilled water. The amplification protocol consisted of 35 cycles of denaturation at 94°C for 30 seconds, annealing at 60°C for 30 seconds and extension at 72°C for 30 seconds. The amplified PCR products were checked for correct size of 279bp by electrophoresis in a 3% agarose gel. The PCR products were subsequently digested with a restriction enzyme *Bcl*1 for 1 h at 50°C and were subjected to electrophoresis in a 3% agarose gel. The resulting band patterns were GG type; single band of 279 bp, AG type; three bands of 279, 157, 122 bp and AA type; two bands of 157 and 122bp as described by Valve et al. (19) (Fig. 1).

Table 1. The general characteristics of the total subjects in this study

	Total subjects (n=248)
Age (year)	28.20±0.50[1)]
Weight (kg)	74.46±0.61
Body mass index (BMI) (kg/m^2)	29.09±0.21
Waist/hip ratio (WHR)	0.925±0.004
Systemic blood pressure (SBP) (mmHg)	119.77±0.79
Diastolic blood pressure (DBP) (mmHg)	74.87±0.65

[1)]Mean±SE.

Biochemical analysis

Blood samples were obtained after fasting overnight for more than 12 h and centrifuged at 2,000 rpm for 10 min. The serums were taken and concentrations of fasting glucose, total cholesterol, HDL cholesterol, triglyceride, GOT, GPT and total bilirubin were measured by auto biochemical analyzer (SP-4410, ARKRAY, Japan). LDL cholesterol was calculated using Friedewald equation [LDL cholesterol=total cholesterol−HDL cholesterol−TG/5].

Statistical analysis

All values were presented as mean±SE. Age-adjusted univariate analysis of variance was performed by General Linear Model procedure to examine the independent effect of UCP-1 genotype on dependent variables. Statistical significance was established at the level of $p<0.05$. All analyses were performed using SPSS ver. 10.0.

RESULTS

The frequencies of the genotypes in UCP-1 A-3826G polymorphism were measured among 248 female overweight subjects. It was shown that AA type was 27.8% (n=69), AG type was 51.2% (n=127) and GG type was 21.0% (n=52), which was in agreement with Hardy-Weinberg equilibrium. The frequency of G allele was 0.47 and was similar to the frequencies reported in other Korean studies which were reported to be 0.46~0.51 (20,21) and also similar to the frequencies in Japanese population which were reported to be 0.46~0.52 (9,13). However it is almost twice than the frequencies reported in Caucasian population, which were reported to be 0.26 for Finnish (19), 0.25 for Danish and German

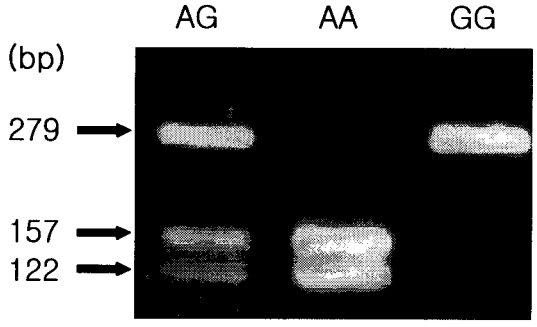

Fig. 1. Polymorphism of the uncoupling protein-1 gene.

(22,23), and 0.23 for Austrian women (12).

Table 2 shows the comparison of physical characteristics and body compositions of the subjects according to the genotypes of UCP-1. Body weight, BMI, WHR, SBP, DBP and body compositions were not significantly different by UCP-1 genotype. For more accurate evaluation of the effects of UCP-1 genotype on body fat accumulation, all subjects were tested using CT to measure the cross-sectional fat areas at abdominal and distal part of the body. An example of CT-measured body fat distribution is shown in Fig. 2. Abdominal visceral fat area was significantly higher in GG type compared with AA and AG type (p=0.009) (Table 3). Abdominal subcutaneous fat area was not significantly different by UCP-1 genotype and total abdominal fat area combining abdominal subcutaneous fat area and visceral fat area was also not significantly different. The visceral fat to subcutaneous fat ratio was higher in GG type compared with other types even though statistical significance was not found. Subcutaneous fat areas in the distal part of the body were measured at upper and lower thigh, which were not significantly different by UCP-1 genotypes.

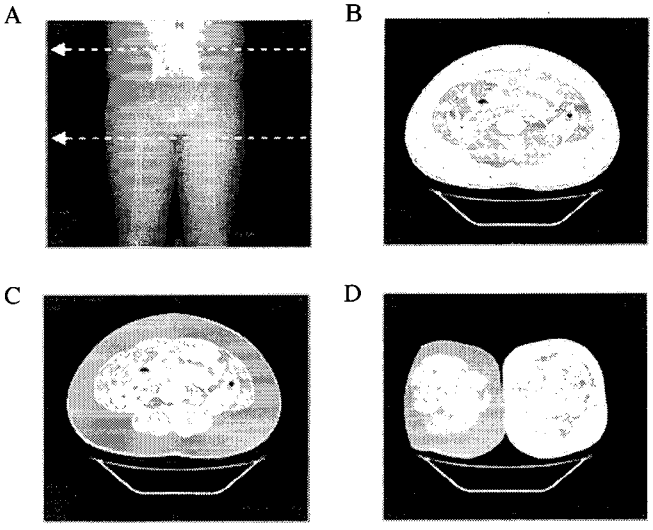

Fig. 2. Measurement of cross-sectional fat area using CT. (A) Abdominal and thigh positions for cross-sectional fat area measurement. (B) An example of total abdominal fat area. (C) An example of visceral fat area. (D) An example of thigh subcutaneous fat area.

Table 4 shows the comparison of serum biochemical characteristics of the subjects by the genotypes of UCP-

Table 2. Comparisons of physical characteristics and body compositions by genotypes of UCP-1

Genotype	AA type (n=69)	AG type (n=127)	GG type (n=52)	p-value[2)]
Physical characteristics				
Weight (kg)	74.52±1.24[1)]	75.18±0.90	72.56±1.36	0.244
BMI (kg/m^2)	29.20±0.50	29.16±0.28	28.93±0.55	0.785
WHR	0.929±0.008	0.926±0.004	0.921±0.009	0.564
SBP (mmHg)	119.52±1.47	119.90±1.28	118.92±1.44	0.656
DBP (mmHg)	74.51±1.25	75.34±1.08	74.47±1.37	0.583
Body composition				
Water (kg)	31.69±0.37	31.88±0.33	31.25±0.40	0.409
Fat mass (kg)	28.63±0.88	29.05±0.54	27.32±1.06	0.289
Lean body mass (kg)	45.90±0.54	46.15±0.46	45.23±0.57	0.399
Percent body fat (%)	38.00±0.57	38.11±0.43	37.20±0.73	0.574

[1)]Mean±SE.
[2)]p-values were obtained by general linear model (covariance) analysis adjusted for age.

Table 3. Comparisons of CT-measured fat areas by genotypes of UCP-1

Genotype	AA type (n=69)	AG type (n=127)	GG type (n=52)	p-value[2)]
Abdominal subcutaneous fat (mm^2)	31847±1280[1)]	31745±837	29198±1366	0.150
Abdominal visceral fat (mm^2)	6389±309	7070±390	7407±271	0.009
Total abdominal fat[3)] (mm^2)	37183±1406	39357±1014	36276±1636	0.122
V/S ratio[4)] (mm^2)	0.220±0.014	0.244±0.011	0.276±0.036	0.280
Upper thigh subcutaneous fat (mm^2)	16555±465	17077±311	16377±548	0.521
Lower thigh subcutaneous fat (mm^2)	11452±404	12213±292	11750±574	0.449

[1)]Mean±SE.
[2)]p-values were obtained by general linear model (covariance) analysis adjusted for age.
[3)]*Total abdominal fat* is the sum of abdominal subcutaneous fat and abdominal visceral fat.
[4)]V/S ratio is the ratio of abdominal visceral fat to abdominal subcutaneous fat.

Table 4. Comparisons of serum biochemical parameters by genotypes of UCP-1

Genotype	AA type (n=69)	AG type (n=127)	GG type (n=52)	p-value[4]
Lipid profiles				
Total cholesterol (mg/dL)	180.45±3.72[1]	181.30±2.63	193.00±4.95	0.103
LDL cholesterol (mg/dL)	110.15±3.09	111.46±2.41	123.63±4.77	0.033
HDL cholesterol (mg/dL)	46.73±1.37	47.03±0.95	46.78±1.67	0.988
Triglyceride (mg/dL)	109.70±4.64	112.88±4.29	115.63±7.25	0.854
Atherogenic index[2]	3.05±0.13	3.01±0.09	3.31±0.16	0.413
LDL/HDL[3]	2.54±0.11	2.49±0.08	2.79±0.14	0.276
Fasting blood glucose				
Glucose (mg/dL)	108.95±4.27	102.15±1.83	107.27±3.60	0.238
Liver function indicators				
Total bilirubin (mg/dL)	0.576±0.024	0.699±0.098	0.581±0.022	0.537
GOT (IU/L)	18.85±0.83	23.03±2.33	23.04±2.87	0.375
GPT (IU/L)	24.77±2.23	30.67±3.16	26.93±3.38	0.384
Albumin (g/dL)	4.39±0.04	4.40±0.03	4.42±0.04	0.567
Protein (g/dL)	7.60±0.06	7.44±0.04	7.53±0.08	0.703

[1]Mean±SE.
[2]Atherogenic index (AI) = (Total cholesterol−HDL cholesterol)/HDL cholesterol.
[3]LDL cholesterol to HDL cholesterol ratio.
[4]p-values were obtained by general linear model (covariance) analysis adjusted for age.

1. Serum LDL cholesterol level was significantly higher in GG type compared with other types (p=0.033). Atherogenic index and LDL/HDL were 8.5~9.8% higher in GG type than other types even though statistical significances were not found. Serum total cholesterol level was also higher in GG type even though statistical significance was not observed. Triglyceride and glucose were not significantly different by UCP-1 genotype. Liver function indicators were also not different by UCP-1 genotypes.

Among all subjects, 121 subjects finished 1 month weight lose program containing hypocaloric diet and exercise and the changes in body weight and BMI during the program were compared by UCP-1 genotypes (Table 5). The BMI changes were -3.30±0.36 kg/m^2 in AA type and -3.06±0.22 kg/m^2 in AG type. In GG type, BMI change was -2.55±0.23 kg/m^2 showing 22.7% decrease compared with AA type even though the results are not statistically different ($p>0.05$). Body weight change showed similar results.

DISCUSSION

Recently, numerous candidate genes were searched to find out the genetic factors implicated in the pathogenesis of obesity and related metabolic disorders. UCP-1 which plays a major role in thermogenesis was suggested to be one of the candidates. Until now many association studies conducted in various populations suggested the association of UCP-1 G allele with higher weight gain, lower weight loss and worse biochemical parameters. Oppert et al. (8) reported that G allele of UCP-1 was associated with higher body weight gain over the 12-year period among 57 French-Canadians. Fumeron et al. (10) suggested an association of the G allele of UCP-1 with lower weight loss after a low caloric diet in 163 French obese subjects. Kogure et al. (9) reported that 113 Japanese obese subjects (BMI 31.0±5.6 kg) were treated with a combined low calorie diet and exercise for 3 months and the decrease in body weight was less in GG type than AA type (4.3±2.6 kg vs 7.4±4.2 kg), although the food intake, exercise and initial BMI were similar in these groups. Even though significant role of UCP-1 polymorphism in obesity and related metabolic disorders has been suggested in many studies, many controversy remains because some reports do not support its role. Urhammer et al. (23) reported that UCP-1 poly-

Table 5. Comparisons of the changes in body weight and BMI during 1 month weight lose program by genotypes of UCP-1

Genotype	AA type (n=32)	AG type (n=68)	GG type (n=21)	p-value[2]
Weight (kg)	-7.09±0.40[1]	-7.30±0.34	-6.41±0.54	0.378
BMI (kg/m^2)	-3.30±0.36	-3.06±0.22	-2.55±0.23	0.325

[1]Mean±SE.
[2]p-values were obtained by general linear model (covariance) analysis adjusted for age.

morphism was not associated with obesity in 380 Danes. In the report of Gagnon et al. (24) UCP-1 genotype was not related to obesity indices in 985 Swedish subjects. The results of this study showed that BMI and body fat mass were not significantly different by UCP-1 genotype (Table 2). The outcome of weight loss program composed of hypocaloric diet and exercise showed that weight and BMI decrease was somewhat lower in GG type compared with AA type even though statistical significance was not found (Table 5). Thus, the role of UCP-1 polymorphism is very complex and controversial until now, because obesity and related metabolic disorders may be determined by environmental and life style factors as well as genetic factors in which many candidate genes and their interactions may be involved.

Until now, however, few researches were conducted about the effects of UCP-1 genotype on CT-measured body fat distribution. Table 3 shows that GG type is associated with significantly increased abdominal visceral fat area ($p=0.009$). UCP-1 is an integral component of the mitochondrial inner-membrane and transports proton across the membrane. As a result, the electrochemical gradient that is generated by electron transport chain dissipates and heat is produced instead of chemical energy (25). Oberkofler et al. (26) reported that UCP-1 mRNA level in visceral fat is significantly lower in obese subjects than lean subjects suggesting a role of UCP-1 in human visceral obesity. A-3826G polymorphism of UCP-1 is located in the 5′-flanking region of the gene, which may cause a difference in its mRNA expression. Esterbauer et al. (6) compared UCP-1 mRNA level in visceral fat tissue by UCP-1 genotypes, and found that G allele was associated with significantly low level of its mRNA. It can be suggested that G allele carrier of UCP-1 gene may have reduced expression of UCP-1 in visceral fat, which cause less energy dissipation as heat and more energy accumulation as a form of fat. The expression level of UCP-1 in subcutaneous fat tissue was reported to be much lower than in visceral fat tissue, and was not significantly different in obese and lean subjects which suggests no significant role of subcutaneous fat UCP-1 expression on obesity (26). Table 3 shows that subcutaneous fat areas of abdomen and thigh were not significantly different by UCP-1 genotype, suggesting that the effect of UCP-1 genotype were different on subcutaneous fat tissue and visceral fat tissue. Low expression level of UCP-1 in subcutaneous fat may cause insufficient phenotype expression of the A-3826G genotype difference in 5′-flanking region of UCP-1, while in visceral fat, with high UCP-1 mRNA level, genotype difference was sufficiently expressed to significant difference in phenotype, i.e. visceral fat area (7,27). UCP-1 expression is known to be activated by beta 3-adrenergic receptor to which expression is lower in subcutaneous fat compared with visceral fat providing some explanation of the difference in UCP-1 mRNA level in subcutaneous and visceral fat tissue (27).

One of the most important features of visceral fat is its draining on the portal vein which supplies blood to the liver. Increased visceral fat tissue causes increased lipolysis of fat and increased level of fatty acid in portal vein. As a result, the liver is exposed to exaggerated supply of fatty acid which is catabolized to acetyl-CoA, a building block of cholesterol biosynthesis. The liver is one of the main organs of cholesterol biosynthesis, and when supplied with excess fatty acid, it will produce more cholesterol and transport it to other tissues leading to the elevation of serum LDL cholesterol level as shown in Table 4.

It should be considered that the relation between obesity and metabolic disorders shows ethnical difference. In Caucasian population, risks of metabolic disorder begin to increase at BMI 25, moderate at BMI 30, and severe at BMI 35. In Asian population, however, metabolic risk begins to increase at BMI 23, moderate at BMI 25, and severe at BMI 30, so differential diagnosis and treatment for obesity-related metabolic disorders are required (28). The different etiology of obesity and metabolic disorders of the Asian population may be related not only to the difference in diet pattern but also to the difference in genetic characteristics, an example of which is the difference of the allele frequencies of UCP-1 gene. G allele frequency is about two-fold higher in Asian than Caucasian population. If the G allele of UCP-1 gene is associated with visceral fat accumulation and resulting metabolic disorders without no significant effect on BMI as shown in this study, it may partly explain ethnical differences in the relation of BMI and metabolic disorders, and it can be hypothesized that higher G allele frequency of the Asian population is one of the genetic factors which leads to higher susceptibility to metabolic disorders compared with Caucasian population in same BMI level (28).

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